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Topical Review

Antibody-Mediated Autoimmune Encephalitis in Childhood

J. Nicholas Brenton MD *, **Howard P. Goodkin MD, PhD**

Division of Pediatric Neurology, Department of Neurology, University of Virginia, Charlottesville, Virginia

ABSTRACT

BACKGROUND: The differential diagnosis of encephalitis in childhood is vast, and evaluation for an etiology is often unrevealing. Encephalitis by way of autoimmunity has long been suspected, as in cases of acute disseminated encephalomyelitis; however, researchers have only recently reported evidence of antibody-mediated immune dysregulation resulting in clinical encephalitis. **MAIN FINDINGS:** These pathologic autoantibodies, aimed at specific neuronal targets, can result in a broad spectrum of symptoms including psychosis, catatonia, behavioral changes, memory loss, autonomic dysregulation, seizures, and abnormal movements. Autoimmune encephalitis in childhood is often quite different from adult-onset autoimmune encephalitis in clinical presentation, frequency of tumor association, and ultimate prognosis. As many of the autoimmune encephalitides are sensitive to immunotherapy, prompt diagnosis and initiation of appropriate treatment are paramount. **CONCLUSIONS:** Here we review the currently recognized antibody-mediated encephalitides of childhood and will provide a framework for diagnosis and treatment considerations.

Keywords: autoimmune, encephalitis, pediatric, encephalopathy

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Introduction

Encephalitis is a broad term encompassing any inflammatory disease process of the brain that manifests clinically with alterations of consciousness and/or behavioral changes. Associated signs and symptoms of encephalitis may include (but are not limited to) seizures, movement abnormalities (e.g., dyskinesias, choreoathetosis), ataxia, dysautonomia, and focal neurological deficits. Encephalitis may occur as the result of a primary infection of the central nervous system (CNS) or through an autoimmune process triggered by an infection, vaccine, or occult neoplasm.

Researchers have long presumed that an autoimmune process has the potential to lead to a clinical encephalitis (e.g., acute disseminated encephalomyelitis [ADEM], opsoclonus-myoclonus ataxia, and Rasmussen encephalitis),[1-3] yet the pathogenic immune mechanisms for many of these cases have never been defined. For the adult-onset encephalitides, particularly those with limbic symptomatology, paraneoplastic autoantibodies (i.e., antibodies formed in association with a neoplasm) were described as early as 1992.[4-6] It was not until the early 2000s that disease-causing, nonparaneoplastic autoantibodies (i.e., those formed without an associated neoplasm) to neuronal surface antigens were officially reported.[7-9] When the California Encephalitis Project was initiated in 1998, an infectious etiology was the most commonly identified cause of reported encephalitis cases.[10] Identified autoimmune-mediated encephalitis cases have now surpassed individual viral etiologies[11]; however, the exact prevalence of individual autoimmune encephalitides remains largely unknown.

Presentation with an autoimmune encephalitis in childhood is often subacute, with a varied constellation of symptoms.[12-14] Concurrent inflammatory findings in the cerebrospinal fluid (CSF), including the presence of oligoclonal bands, lymphocytic pleocytosis, and elevated protein, may be present but are relatively nonspecific. Magnetic resonance imaging (MRI) of the CNS may also demonstrate abnormalities that provide clues for diagnosis, particularly on fluid-attenuated inversion recovery (FLAIR) or T2-

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* Communications should be addressed to: Dr. Brenton; Division of Pediatric Neurology; Department of Neurology; University of Virginia; PO Box 800394; Charlottesville, VA 22908.
E-mail address: jnb8h@virginia.edu

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weighted images. The treatment of autoimmune encephalitis consists of immunomodulatory therapy. The duration of therapy depends on the autoimmune encephalitis in question and the patient's clinical response. Outcome in childhood is generally good but may depend on the pathogenic autoantibody and neuronal target involved, in addition to the time from symptom onset to treatment initiation.

This review discusses the spectrum of known autoimmune encephalitides occurring in childhood, with a primary focus on those disorders whose associated autoantibodies target either the neuronal surface or intracellular proteins (Table 1). We will describe the clinical presentation, laboratory and imaging findings, and outcomes for both common and rare autoimmune encephalitides and include a discussion on the use of immunotherapy to treat autoimmune encephalitis.

Unique aspects of autoimmune encephalitis in childhood

Although several aspects of autoimmune-based encephalitis can be generalized across the age spectrum (e.g., symptomatology and acute management), the clinical presentation, disease course, impact of a chosen therapy,

TABLE 1.
Clinical Characteristics of Individual Antibody-Associated Encephalitides in Childhood

Autoimmune Encephalitis	Ages Described*	Clinical Manifestations	Associated Tumor	Risk of Relapse	Long-Term Outcomes
NMDAR	20 mo-17 yr	Seizures, behavioral disturbance, aphasia, psychosis, orofacial dyskinesias, catatonia	30% of females with ovarian teratoma	Up to 25% when causative tumor is not identified and removed	80% or greater have full recovery
VGKC	10 mo-17 yr	Seizures, behavioral disturbance, movement disorders, dysarthria, developmental regression	Neuroblastoma in one case (patient with multiple autoantibodies)	Unknown; reported in single case series as 25% relapse rate in childhood	Unknown, but most reported patients show marked to full recovery
GlyR	1-14 yr	PERM, seizures, ADEM with ON	None currently reported in childhood	Unknown; reported in single case series as 25% relapse rate in childhood	Unknown; generally considered to have good outcomes
$GABA_A$	2-17 yr	Seizures, cognitive and memory alterations, movement abnormalities	Hodgkin's lymphoma predating encephalitis in one patient	Unknown, but reported in a single pediatric case	Unknown; most have good recovery but residual seizures
$GABA_B$	3-18 yr	Seizures, movement disorders, memory loss, delirium, psychosis	None currently reported in childhood	Unknown in childhood	Unknown; majority reported show full recovery
AMPA	7-8 yr	Seizures, memory loss, behavioral changes	None currently reported in childhood	Unknown in childhood	Unknown
D2R	4 mo-15 yr	Seizures, lethargy, psychiatric symptoms, dystonia, parkinsonism, chorea, ataxia	None currently reported in childhood	Unknown; reported in case series as 25% relapse rate in childhood	Unknown; a single case series reports full recovery in 40%
mGluR5 (Ophelia syndrome)	Adolescence	Memory loss, depression, hallucinations, behavior abnormalities	Hodgkin's lymphoma	Uncommon if treated appropriately	Full recovery with appropriate treatment
Hu	1-15 yr	Behavioral changes, seizures, posterior cord syndrome, ataxia	Estimated 25% associated with neuroblastoma	Unknown in childhood	Reported patients with continued seizures despite treatment
Ma1 and *Ma2*	2-14 yr	Seizures, behavioral changes, memory loss, speech changes	None currently reported in childhood	Unknown in childhood	Reported patients with poor outcomes
GAD	2-17 yr	Seizures, cognitive decline, psychosis, memory loss, stiff-person syndrome, progressive developmental delay	None currently reported in childhood	Unknown in childhood	Variable outcome potentially related to rapidity of treatment

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
AMPA = α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
D2R = Dopamine D2 receptor
$GABA_A$ = Gamma-aminobutyric acid type A
$GABA_B$ = Gamma-aminobutyric acid type B
GAD = Glutamic acid decarboxylase
GlyR = Glycine receptor
mGluR5 = metabotropic glutamate receptor 5
NMDAR = N-methyl-D-aspartate receptor
ON = Optic neuritis
PERM = Progressive encephalomyelitis with rigidity and myoclonus
VGKC = Voltage-gated potassium channel

* Ages listed include those age ranges for children and adolescents, although it is important to remember that all disorders in this table have been reported in adulthood as well.

and ultimate outcome are often distinctly different in the pediatric population. Although many of the autoimmune encephalitides have a similar symptomatology regardless of age of onset, the presenting feature(s) of pediatric-onset and adult-onset forms of a given autoimmune encephalitis may be quite different. For example, in anti–N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, children are more likely to have a neurologic-based presentation (consisting of movement abnormalities and/or seizures) than are adults, who tend to present with psychiatric features.[15] In particular, younger children may exhibit symptoms quite different from those seen in adolescents or adults, including developmental regression, temper tantrums, and inattention.[16,17]

In adults, autoimmune encephalitis is commonly paraneoplastic—i.e., accompanied by the presence of an occult tumor that serves as a stimulus for autoantibody production. In childhood, nonparaneoplastic, antibody-associated encephalitis is more commonly diagnosed. In spite of this, because paraneoplastic encephalitis has been reported in children, searching for the neoplasms underlying many of the well-characterized autoimmune encephalitides remains essential.[18]

Finally, when managing a pediatric patient one must weigh the long-term implications of each treatment. It is important to consider the potential effect of a given immunotherapy on the developing neuroimmunologic system. Although the risks of first-line immunotherapies used to treat acute manifestations of autoimmune disease are typically justified, the beneficial use of long-term, steroid-sparing immunotherapeutic agents must be carefully considered, taking into account the patient's age and the risk of disease recurrence. Pursuing chronic immunosuppression requires a candid discussion with the family about the influence of long-term therapy on fertility and the risk of future malignancy.

Pediatric autoimmune encephalitides with antibodies targeting neuronal cell surface antigens

Anti-NMDAR encephalitis

After the discovery of its pathogenic autoantibody in 2007, anti-NMDAR encephalitis has become a well-recognized autoimmune, inflammatory syndrome.[19] To date, >400 cases have been described in children and adolescents, including those as young as 8 months of age.[11,14,20-26] An estimated 40% of all reported patients are younger than 18 years, and young women constitute 80% of all pediatric cases.[14] Although the exact prevalence of this entity has yet to be determined, large-scale studies in both the United Kingdom and Australia have shown anti-NMDAR encephalitis to be the leading identified cause of antibody-mediated autoimmune encephalitis.[27,28] In addition, the California Encephalitis Project found that in young adults, anti-NMDAR encephalitis was a leading entity among all cases of encephalitis with known etiology.[11]

The NMDA receptors are glutamate-gated cationic channels found throughout the brain that play an important role in synaptic transmission and plasticity. These diheteromeric and triheteromeric structures are composed of two GluN1 subunits in combination with either two GluN2 subunits or a GluN2 and a GluN3 subunit. Autoantibodies of immunoglobulin G (IgG) subclass G1 bind the extracellular domain of the GluN1 subunits, resulting in antibody-mediated capping and internalization of surface NMDA receptors. The presence of the autoantibody is correlated with a reversible decrease in the surface expression of these receptors.[29,30] The loss of receptors reduces NMDAR-mediated synaptic function, resulting in the unique clinical manifestations of the disease.

The clinical phenotype of anti-NMDAR encephalitis evolves through several stages of disease progression. In approximately 50% of patients, a prodromal phase is evident days to weeks before disease onset and may consist of fever, malaise, headache, and/or symptoms of gastrointestinal or upper respiratory illness.[14,31] This prodrome is followed by psychiatric (delusions, hallucinations, paranoia, insomnia, agitation) and neurological (seizures, speech impairment, ataxia, abnormal movements, autonomic instability) symptoms. Younger patients tend to present with seizures and abnormal movements, whereas adults typically present with psychiatric manifestations.[15] In spite of the influence of age of onset on presenting symptoms, most cases ultimately evolve into a similar syndrome that contains a mixture of varied neurological and psychiatric manifestations.

Seizures are eventually present in up to 80% of patients.[14,15] Seizures may appear focal or generalized at onset, and status epilepticus has been reported.[12,17,32] The vast majority of patients (90% to 100%) have an abnormal electroencephalograph (EEG), typically showing focal or diffuse slowing and/or epileptiform discharges.[14,31] An EEG pattern known as *extreme delta brush* has been described in anti-NMDAR encephalitis and may be detected in up to 30% of adult patients.[31,33] This EEG pattern, though not pathognomonic, may support a diagnosis of anti-NMDAR encephalitis.

Hyperkinetic movements are frequently noted in pediatric anti-NMDAR encephalitis and include dyskinesias, choreoathetosis, tremor, and dystonia.[34] Orofacial dyskinesias are commonly seen and consist of semirepetitive grimacing, chewing, or biting movements.[12] Continuous video-EEG monitoring may assist in excluding an epileptic etiology as the cause of these paroxysmal movements. Signs of autonomic dysfunction, including hyperthermia, tachycardia, hypertension, urinary incontinence, central hypoventilation, and cardiac dysrhythmia, occur in about 40% of preadolescent children and 50% of adolescents.[15]

Brain MRI in anti-NMDAR encephalitis demonstrates abnormalities in less than half of all pediatric patients.[14,15] If present, these imaging findings are relatively nonspecific and may include cortical and/or subcortical, basal ganglia, and infratentorial T2 hyperintensities with or without transient meningeal enhancement.[19,22] In addition, children with a primarily demyelinating appearance on MRI have been reported, some with imaging features mimicking those found in neuromyelitis optica,[35] ADEM,[36] and multiple sclerosis.[37-39] The extent and location of imaging abnormalities does not appear to have a reliable correlation with clinical course.[15]

Evaluation of a child with suspected anti-NMDAR encephalitis should include both serum and CSF analysis to detect the presence of pathogenic anti-NMDAR autoantibodies. Antibody testing is more sensitive in the CSF than

in the serum, with up to 7% of patients demonstrating positive CSF titers with concurrent negative serum titers.[40] The CSF antibody titers correlate strongly with the clinical disease course and remain elevated in those who experience a relapse or do not show primary clinical improvement.[40]

Anti-NMDAR encephalitis can be associated with an underlying tumor that stimulates the production of anti-NMDAR antibodies. An ovarian teratoma is the most commonly associated tumor and is reported to be present in over half of adult female cases.[12] If an associated tumor is discovered, complete tumor resection is important for maximal recovery.[12,15,22] Though not as common in pediatric anti-NMDAR encephalitis, a unilateral or bilateral ovarian teratoma is discovered in approximately 30% of girls aged 18 years or younger.[14] In those aged less than 14 years, the prevalence of ovarian teratoma is <10%.[14] Given this association, all female patients should undergo MRI of the abdomen and pelvis in search for an ovarian teratoma. Testicular teratoma in male patients is rare and has not yet been reported in pediatric cases of anti-NMDAR encephalitis.[15] Extraovarian tumors can occur but are much more common in older adult cohorts.[15]

Time-sensitive treatment with tumor removal (if one is present) and prompt immunotherapy appears to improve patient outcome.[15] First-line immunotherapy includes high-dose intravenous corticosteroids, intravenous immunoglobulin (IVIg), plasma exchange (PLEX), or a combination of the above. In spite of appropriate first-line treatment, up to 35% of pediatric patients do not respond adequately.[14,31] These patients often require more-potent second-line therapies, which carry a greater risk of adverse events. These second-line therapies most commonly include rituximab, a B-cell–depleting monoclonal antibody, and/or cyclophosphamide, an alkylating agent that interferes with DNA transcription.[13]

Although recovery is typically protracted, the clinical outcome is often good in children and young adults. Up to 80% of patients have substantial or full recovery, with reports of gradual, continuing improvement noted up to 2 years after presentation.[15] Clinical relapse occurs in up to 25% of patients, independent of age of onset, and may occur months after the initial clinical manifestations.[14] As such, young women who have recovered from anti-NMDAR encephalitis should undergo yearly tumor surveillance imaging even in the absence of a tumor at disease onset.[13] How long to follow tumor-negative, anti-NMDAR patients with imaging surveillance remains unknown. Given relapse rates of 12% to 25%,[12,14,15,22] tumor-negative patients may require maintenance immunosuppression with a steroid-sparing agent (e.g., mycophenolate mofetil or azathioprine) for up to 1 year. The effect of long-term immunosuppression on the risk of relapse is not known.[41]

Voltage-gated potassium channel complex encephalitides

Voltage-gated potassium channels (VGKCs) are tetrameric signaling complexes tightly associated with auxiliary proteins, including leucine-rich, glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (Caspr2). The vast majority of reported VGKC-complex autoantibodies appear to be targeted at one of these protein components rather than those at the potassium channel itself.[42,43] Like NMDAR autoantibodies, anti–LGI1 and anti–Caspr2 antibodies are typically identified via antigen-specific cell-based assays[43]; however, when these specific autoantibodies are not detected, high titers (>400 pM) of VGKC-complex antibodies detected by radioimmunoassay may be relevant in the appropriate clinical context.[44] It is important to recognize that the presence of VGKC-complex antibodies as measured by radioimmunoassay is nonspecific, as it has been reported in a number of varied immune-mediated and nonimmune-mediated neurological disorders. High titers of these VGKC-complex antibodies, at best, appear to be nonspecific biomarkers of inflammatory neurological disease, but they currently do not appear to provide specific diagnostic utility.[45]

Autoantibodies to the VGKC complex have been reported in adult patients with limbic encephalitis, typically manifesting with short-term memory loss, cognitive changes, and seizures. These antibodies can be paraneoplastic in origin in up to a third of adult patients, with associated adenomas, carcinomas, thymomas, and hematologic malignancies.[46] This autoimmune entity has not been defined as clearly in the pediatric population, although existing case reports and small case series suggest varied clinical manifestations. Most presentations are characterized by subacute cognitive and memory decline, medically refractory seizures or status epilepticus, and psychiatric symptoms.[47-54] Presenting symptoms may also include developmental regression, movement disorders, and dysarthria.[47]

Cerebrospinal fluid profiling is typically normal but may show evidence of pleocytosis and elevated protein.[48,49,54] MRI may demonstrate increased T2/FLAIR signal in the mesial temporal lobe, along with cortical and/or subcortical hyperintensities.[47-49,54] The frequency of association with neoplasm in children with VGKC-complex autoantibodies remains unknown; however, there are currently no published reports of childhood neoplasm in isolated anti–VGKC-complex encephalitis.

As most reported cases manifest with seizures and/or status epilepticus, antiseizure medications are often employed, with varied success at controlling the seizures. Immunotherapy has been used in cases of identified pediatric VGKC-complex encephalitis, though often with a prolonged latency between symptom onset and treatment. Studies of treatment with high-dose corticosteroids, IVIg, PLEX, and cyclophosphamide report subsequent clinical improvement in 75% to 100% of children.[47-51,53,54] There are minimal data available on long-term outcomes in children, although it appears that early treatment may improve ultimate recovery.[47]

Anti-glycine receptor encephalitis

Glycine receptors (GlyRs) are inotropic receptors that flux chloride, mediating inhibition predominantly in the spinal cord and brainstem. Autoantibodies to the α1 subunit of GlyR have been reported in only a few childhood cases.[55] The clinical presentation of patients with this antibody is consistent with that of stiff-person syndrome and progressive encephalomyelitis with rigidity and myoclonus (PERM); presumably, this results from the autoantibody's primary effect on the brainstem and spinal cord. Patients

with anti-GlyR antibodies may also present with a limbic encephalitis or epileptic encephalopathy. A child with ADEM with optic neuritis in association with anti-GlyR antibodies has been reported.[55] Cumulative data suggest that anti-GlyR encephalitis is not typically paraneoplastic, though in rare cases a tumor is present. In addition, these autoantibodies occur concurrently with glutamic acid decarboxylase (GAD) autoantibodies in some patients. Treatment often involves therapy with corticosteroids, IVIg, and PLEX, and clinical relapses can occur.[55]

Anti-gamma-aminobutyric acid type A receptor encephalitis

Gamma-aminobutyric acid type A ($GABA_A$) receptors are predominantly postsynaptic receptors that mediate both fast phasic (i.e., synaptic) and prolonged tonic (i.e., extrasynaptic) inhibition; $GABA_A$ receptor–mediated inhibition is the predominant form of neurotransmitter-mediated inhibition in the forebrain. Studies have reported autoantibodies against $GABA_A$ receptors in the serum and CSF of a small number of pediatric patients ranging from 2 to 17 years of age at disease onset.[50,51] Clinical presentation of these patients included seizures or status epilepticus, cognitive/memory alterations, and movement abnormalities. MRIs of these patients have demonstrated multifocal, cortical–subcortical T2/FLAIR hyperintensities throughout the CNS, with generalized slowing and/or epileptiform discharges on EEG. Treatment response to immunomodulation has not been defined; however, most reported patients (two of which did not receive immunotherapy) experienced substantial recovery.[56,57]

Anti-gamma-aminobutyric acid type B receptor encephalitis

Gamma-aminobutyric acid type B ($GABA_B$) receptors are metabotropic receptors linked via G proteins to potassium channels. Based primarily on clinical data from adult cases, anti-$GABA_B$ receptor encephalitis often presents with memory loss, confusion, seizures, and, potentially, ataxia.[58,59] Half of adult cases have an associated small-cell lung carcinoma. Oncologic treatment in conjunction with early immunotherapy typically results in good recovery.[59] Anti-$GABA_B$ receptor encephalitis has been reported in a few adolescent females presenting with seizures, psychiatric symptoms, and memory changes. These patients exhibited a good response to immunotherapy, with good outcomes.[59,60]

Anti–α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) is an ionotropic glutamate receptor formed from four subunits that is important for synaptic plasticity, memory, and learning. Autoantibodies targeting the glutamate receptor 1 (GluR1) or glutamate receptor 2 (GluR2) subunits of the AMPAR may result in clinical encephalitis. To date, 35 patients (mostly adults) with anti-AMPAR encephalitis have been described. Adult-onset cases typically manifest with personality changes, memory loss, confusion, seizures, and psychosis. Most adult cases are associated with neoplasm (including small-cell lung cancer, thymoma, ovarian teratoma, and breast cancer), and appropriate immunotherapy and tumor treatment may lead to marked clinical improvement.[61,62] Clinical relapse has been reported in adult cases; however, the true rate of relapse in anti-AMPAR encephalitis is unknown due to the small number of published cases. Long-term outcomes are also unknown because of the lack of longitudinal data. Two reported cases of pediatric anti-AMPAR encephalitis manifested with seizures/status epilepticus, behavioral changes, and memory loss,[63] but this report did not divulge tumor association and outcomes.

Anti-dopamine D2 receptor encephalitis

The role of surface antibodies targeting the extracellular domain of the dopamine D2 receptor (D2R), an essential receptor modulating dopaminergic transmission, has been investigated in cases of encephalitis associated with movement disorders.[64] A case series identified the presence of these potentially pathogenic anti-D2R antibodies in 12 of 17 pediatric patients (median age of 5.5 years) with basal ganglia encephalitis. The clinical presentation included lethargy, psychiatric symptoms, and abnormal movements (dystonia, parkinsonism, chorea, or ataxia). MRIs showed T2/FLAIR hyperintensities within the basal ganglia in half of the D2R-positive cohort, but the EEG was typically normal. These antibodies have also been discovered in a small number of patients with Tourette syndrome and Sydenham chorea. Response to therapy remains uncertain; however, patients treated promptly after diagnosis have shown clinical improvements.[64] This preliminary work has yet to be replicated within the literature; thus, the significance and pathogenicity of these antibodies remains in question.

Ophelia syndrome

This clinical entity, first described in a 15-year-old girl, is a unique but very rare form of autoimmune encephalitis associated with underlying Hodgkin's lymphoma. The syndrome is characterized by progressive memory loss, depression, hallucinations, and bizarre behavior. Recent reports of cases of Ophelia syndrome identify a potentially pathogenic autoantibody against metabotropic glutamate receptor 5 (mGluR5), which is abundantly expressed within the hippocampus.[65] Full recovery is typical with immunotherapy and appropriate treatment of the underlying lymphoma.[65]

Interestingly, autoantibodies targeting metabotropic GluR1 have been reported in three adult cases associated with subacute cerebellar ataxia.[66,67] In two of these cases (one of which involved a 19-year-old patient), neurological symptoms developed while the patients were in remission from previously treated Hodgkin's lymphoma.[67] In these cases, the brain MRI may be normal but may also show evidence of diffuse cerebellar hyperintensities on FLAIR and diffusion sequences.[66] Treatment of the young patient with corticosteroids and with PLEX resulted in gait improvement and concurrent reduction in mGlurR1 antibody titers. Antibodies to metabotropic GluR1 have not been described in young children.

Pediatric autoimmune encephalitides with autoantibodies targeting intracellular antigens

Anti-Hu encephalitis

Antineuronal nuclear antibody type 1, also known as anti-Hu, is a marker of paraneoplastic autoimmunity associated with small-cell carcinoma in adults. Serologic immunohistochemistry shows binding of this autoantibody to neuronal nuclei throughout the central and peripheral nervous system.[68] Anti-Hu encephalitis is rare in the pediatric age group.[48,69] In children, anti-Hu antibodies have been most frequently described in the setting of underlying neuroblastoma; however, cases of limbic encephalitis without associated malignancy have been reported. These cases typically present with behavioral changes, memory loss, and seizures. In children, oncologic association is more often the exception than the rule.[48,69-71]

As opposed to encephalitides associated with neuronal surface antigens exhibiting an antibody-/complement-mediated immune response, encephalitis associated with intracellular antigens (namely anti-Hu and anti-Ma) appears to be associated with T-cell–mediated neuronal cytotoxicity.[72] Anti-Hu encephalitis typically demonstrates a poor response to immunotherapy. Furthermore, most children and adolescents who have experienced anti-Hu encephalitis often have refractory epilepsy in addition to cognitive impairment.[69] The T-cell–mediated cytotoxicity, in conjunction with the intracellular antigenic location, may help to explain the poor response to treatment and poor outcomes. Early utilization of immunotherapeutic agents that primarily target T-cell populations is advised, although the effect of this strategy on long-term outcomes is unknown.

Anti-Ma2 encephalitis

Ma2 (also referred to as Ta) is an intracellular protein that is expressed in the neurons of the brain, spinal cord, dorsal root ganglia, intestinal autonomic neurons, and adrenal medullary ganglion cells.[6] Anti-Ma2 encephalitis is a rare paraneoplastic disorder that preferentially involves the limbic system, diencephalon, and upper brainstem. Cases are mostly confined to adulthood and have been associated with testicular germ cell tumors, non-small-cell lung cancer, and breast cancers.[73] Only a few cases of anti-Ma2 encephalitis have been reported in children.[48,71] Reported pediatric cases presented with subacute onset of focal seizures, behavioral changes, speech disturbance, and dystonia. Imaging findings are relatively nonspecific and varied. Although anti-Ma encephalitis is typically associated with a neoplasm in adult cases, the reported pediatric cases are not associated with tumor.

Like other autoimmune encephalitides that target intracellular neuronal proteins, this encephalitis is associated with a primarily cytotoxic T-cell–mediated response.[72] First-line treatment often consists of corticosteroids, IVIg, and/or PLEX (with oncologic therapy if a tumor is identified), although early use of T-cell–targeting immunotherapy appears logical. Clinical outcome is typically poor, with medically refractory seizures.[48,71]

Anti-GAD–associated encephalitis

Glutamic acid decarboxylase (GAD) is an intracellular enzyme responsible for the synthesis of the inhibitory neurotransmitter GABA. It is selectively expressed in GABAergic neurons and in pancreatic β-cells and is considered a major autoantigen in type 1 diabetes mellitus.[74] Studies have found GAD autoantibodies in a number of neurological disorders including stiff-person syndrome, cerebellar ataxia, autoimmune epilepsies, and limbic encephalitis. In addition, GAD autoantibodies often coexist with other pathogenic autoantibodies (e.g., anti-$GABA_B$), further confounding the role of these antibodies in a disease process.[58]

Patients from 2 to 17 years of age with high titers of anti-GAD in the CSF have manifested with focal seizures (often arising from the temporal lobe), cognitive and memory decline, progressive developmental delay, and psychiatric symptoms. The CSF may appear normal, although up to 50% of reported cases have demonstrated the presence of oligoclonal bands. The MRI and EEG may show abnormalities arising from the mesial temporal structures.[48,75-78] Treatment with immunotherapy results in variable outcomes that may depend on time from onset to immunotherapy initiation. Several pediatric patients have had persistent memory impairment and seizures in spite of immunotherapy treatment.[48]

Evaluation and therapeutic approach for suspected autoimmune encephalitis

Encephalitis by way of autoimmunity should be considered in the differential diagnosis of any pediatric patient presenting with unexplained encephalopathy of acute or subacute onset. When electing to send a commercial panel that tests for the individual autoantibodies implicated in pediatric autoimmune encephalitis, the clinician should strongly consider sending both serum and CSF. CSF testing for IgG GluN1 (NMDA subunit) antibodies has been shown to be more sensitive than serologic testing, and the presence of autoantibodies within the spinal fluid is often helpful in demonstrating intrathecal autoantibody synthesis.[40] With some testing methods, there is an increased risk for false-positive results of serum samples, and it becomes difficult to interpret positive results when it is only the serum that is tested.[79] These autoantibody tests must always be considered in the context of the patient's clinical symptoms, and caution must be used in the interpretation of weakly positive serologic testing with negative (or untested) CSF.

Given that most imaging and laboratory testing (with the exception of autoantibody testing) is relatively nonspecific, clinicians should eliminate other etiologies while confirmatory autoantibody tests are being processed. The differential diagnosis in pediatric autoimmune encephalitis is broad and includes CNS infection, toxic/drug ingestion, inborn errors of metabolism, primary psychiatric disease, CNS vasculitis, or neoplastic disease (Table 2).

Several features that may support suspicion of an autoimmune etiology include CNS inflammation (CSF pleocytosis, presence of oligoclonal bands, or elevated IgG index), MRI abnormalities including increased T2/FLAIR signal within the mesial temporal lobes, and a clinical response to

TABLE 2.
Differential Diagnosis of Encephalopathy and Encephalitis of Childhood

Infectious etiologies

Viral Encephalitis (e.g., EBV, HHV-6, VZV, HSV, HIV, enterovirus, arbovirus, parechovirus)
Bacterial encephalitis (e.g., *Bartonella*, *Mycoplasma*, *Rickettsia*)
Spirochetal encephalitis (e.g., *Borrelia*)

Toxic

Neuroleptic malignant syndrome
Drug Ingestion (e.g., alcohol, ketamine, phencyclidine, organophosphates)

Epileptic disorders

Nonconvulsive status epilepticus
Fever-induced refractory epileptic encephalopathy in school-aged children (FIRES)

Vascular disorders

Posterior reversible encephalopathy syndrome (PRES)
Inflammatory vasculitis (e.g., primary CNS vasculitis, systemic lupus erythematosus with neuropsychiatric features, Bechet's)
Migraine (e.g. acute confusional migraine)

Miscellaneous disorders

Autism spectrum disorders
Kleine–Levin syndrome

Genetic and metabolic disorders

Inherited disorders and inborn errors of metabolism (e.g., Wilson disease, PKAN, glutaric aciduria type I, Lesch–Nyhan syndrome, creatine transport deficiencies, urea cycle disorders)
Mitochondrial disorders (e.g., Leigh syndrome)

Psychiatric disorders

Brief reactive psychosis
Major depressive disorder with psychotic episode(s)
Conversion disorder

Autoimmune and inflammatory disorders

Demyelinating disease (MS, NMO, ADEM)
Sydenham chorea
Opsoclonus–myoclonus ataxia syndrome
Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT)
Antibody-mediated encephalitides

Structural disease

Neoplasm (e.g., gliomatosis cerebri)
Hydrocephalus

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
CNS = Central nervous system
EBV = Epstein–Barr virus
HHV = Human herpesvirus
HIV = Human immunodeficiency virus
HSV = Herpes simplex virus
MS = Multiple sclerosis
NMO = Neuromyelitis optica
PKAN = Pantothenate kinase-associated neurodegeneration
VZV = Varicella zoster virus

administration of immunotherapy. Ancillary testing with EEG (particularly if an extreme delta brush pattern is noted in suspected anti-NMDAR encephalitis) may prove useful. In addition, the presence of elevated CSF neopterin may serve as a useful marker of inflammation and may be a more sensitive marker of inflammation than CSF pleocytosis.[80] Once the clinician highly suspects a diagnosis of autoimmune encephalitis or confirms it by way of autoantibody testing, he or she should commence appropriate treatment with immunologic agents. The utility of serial CSF and/or serum autoantibody titers as a marker of treatment response and final outcome has yet to be determined.

Acute treatment

To date, no formal comparative, prospective trials have assessed the relative efficacy of individual autoimmune therapies in the acute treatment of the autoimmune encephalitides. Perhaps the greatest insight with regard to the treatment of the autoimmune encephalitides arises from relatively recent work completed in both adults and children with anti-NMDAR encephalitis. Although a data-driven treatment algorithm is not available, we have learned that timing from onset of disease manifestation to the initiation of immunotherapy influences ultimate clinical recovery. Given this, a clinician treating an individual with suspected autoimmune encephalitis must consider rapid treatment with immune therapy after sufficiently ruling out infectious and oncologic entities.

The Figure illustrates a generalized approach to the diagnosis and acute treatment of autoimmune encephalitis. Accepted first-line therapy for every autoimmune encephalitis includes high-dose corticosteroids, IVIg, PLEX, or a combination of these therapies. Although PLEX is often reserved for severely affected patients because of its relative invasiveness, it appears safe, with few adverse effects.[84] If an associated tumor is identified, oncologic management (preferably with resection) is important for ultimate recovery.[12,15]

Some patients with autoimmune encephalitis do not adequately respond to first-line therapies and thus often require advanced treatment options.[15,85] When the clinician concludes that first-line therapies have failed a patient, he or she should escalate to second-line agents (rituximab, cyclophosphamide). In anti-NMDAR encephalitis, second-line therapy is more commonly required in patients

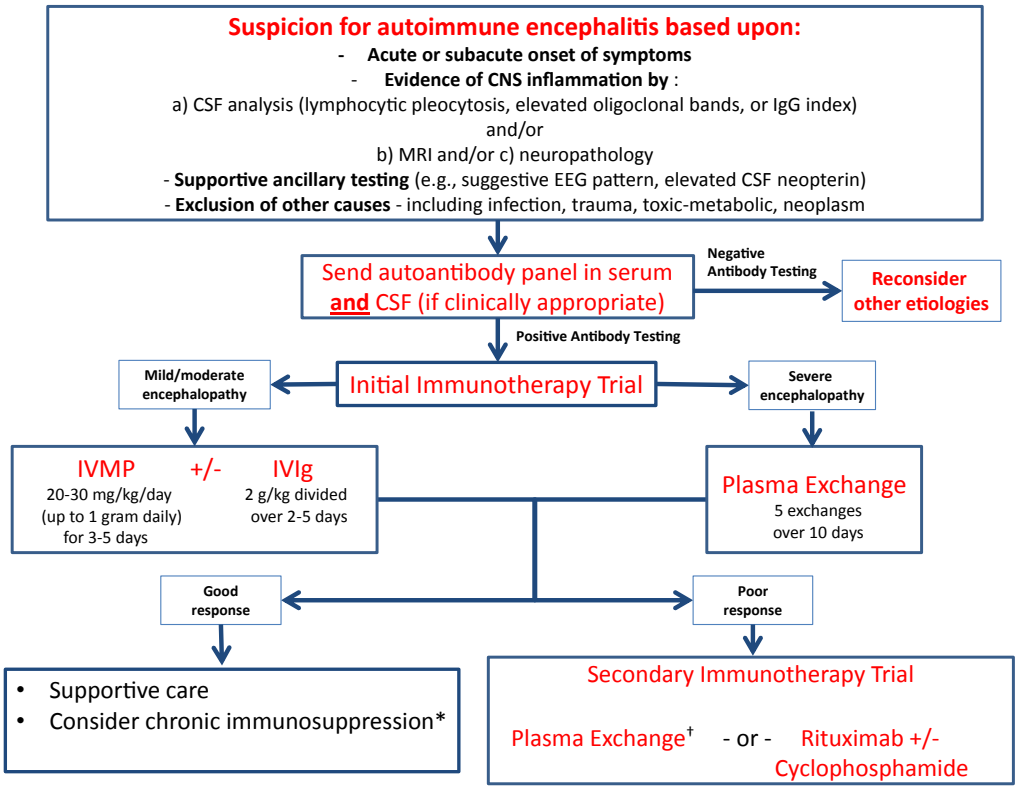

FIGURE.
Proposed acute treatment algorithm for suspected autoimmune encephalitis secondary to neuronal surface antigens.[81-83] This algorithm describes a management approach to pediatric patients with CNS syndromes and the presence in serum or cerebrospinal fluid of antibodies directed against neuronal surface proteins, and it is intended as a general guideline. Individual patients may need a personalized approach based on that individual's clinical phenotype. *Chronic immunosuppression should be considered only in individuals with a suspected propensity for relapsing disease. †PLEX can be considered second-line therapy in individuals who did not receive it as first-line therapy. CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalograph; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; kg, kilograms; mg, milligrams; MRI, Magnetic resonance imaging; PLEX, plasma exchange. (The color version of this figure is available in the online edition.)

lacking an associated ovarian teratoma. In addition, treatment with second-line therapies appears to be predictive of a good outcome and may lower the risk of relapse.[15,86] Clinicians should discuss side-effect profiles of second-line agents with the family unit before administration. Rituximab, though generally considered safe in pediatric autoimmune disease, entails risks of infusion-related reactions and serious infections.[87] The side-effect profile of cyclophosphamide, which often limits its use in children, includes gastrointestinal upset, alopecia, amenorrhea, osteoporosis, hemorrhagic cystitis, and the risk of secondary malignancy and infertility in both males and females.

Chronic treatment

To date, no formal studies have assessed the need for or utility of using chronic immunosuppression in patients who initially respond to acute treatment. Chronic immunosuppression (e.g., mycophenolate mofetil, azathioprine) should be considered only in autoimmune syndromes with a known risk for relapsing disease (e.g., anti-NMDAR encephalitis without an identified ovarian teratoma). In instances where chronic immunosuppression is used to theoretically reduce the risk of relapse, the duration of adequate immunosuppression remains unknown and debated. As long-term data regarding the utility of chronic immunosuppression are lacking, the treating clinician must always analyze the short-term and long-term risks and benefits of a given approach and discuss them with patients and their families.[41]

Future directions and conclusions

The medical community has experienced a significant growth in the recognition, evaluation, and treatment of the autoimmune encephalitides. Armed with the ability to identify and classify pathogenic antibodies formed against neuronal antigens, researchers will undoubtedly add to the list of disease-causing autoantibody syndromes. The frequency of clinical encephalitis patients with autoimmune etiologies now rivals the frequency of those with known viral etiologies.[11] In addition, there is a recognized link between infection and subsequent brain autoimmunity, best illustrated by individuals who develop anti-NMDAR encephalitis after having herpes simplex encephalitis.[88] The importance of considering autoimmune pathogenesis in the differential diagnosis of an encephalitis of unknown etiology cannot be understated, as early recognition and treatment may affect ultimate outcome. Furthermore, understanding the various causes of autoimmune encephalitis in childhood is important for guiding an appropriate diagnostic evaluation and providing a framework for prognostic discussions with the family.

Prompt, adequate therapy with immunomodulatory or immunosuppressant medications is essential for ultimate recovery. Clinicians should administer first-line therapies as soon as they highly suspect or confirm a diagnosis of autoimmune encephalitis. Although associated tumors are more commonly the exception than the rule in pediatric disease, clinicians should search for an underlying malignancy, taking into account the autoimmune entity involved. Second-line immunotherapy is often useful in individuals who do not respond to adequate therapy with first-line treatments. Once the disease is appropriately treated, long-term immunosuppression should be considered in cases where relapse is a significant concern; however, the risks and benefits of long-term immunosuppression in a child need to be carefully considered.

To that end, robust, prospective, randomized controlled trials are needed to better determine the appropriate acute treatment approach to autoimmune encephalitis and to weigh the need for and/or benefits of chronic immunosuppression. Drug trials in children face unique ethical constraints, particularly in the consideration of a placebo-controlled trial design. A combined international effort will be needed to recruit an adequate number of pediatric patients, as the relative rarity of these individual diseases will have an obvious impact on a given study's power and design.

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In the last analysis, we see only what we are ready to see, what we have been taught to see. We eliminate and ignore everything that is not part of our prejudices.

Jean Martin Charcot